REVIEW ARTICLE

Progression of retinopathy in persons with type 2 diabetes: new data, same conclusions?

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KEY WORDS

diabetic retinopathy, glycemia, type 2 diabetes

ABSTRACT

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial was designed primarily to examine the effects of intensive glycemic control on cardiovascular events in persons with type 2 diabetes who were, for additional reasons, at high risk for such events. The trial also examined effects on the same endpoints of intervention on blood pressure and on serum lipids. The study intervention on glycemic control was stopped early because of the effects of this intervention on mortality. The trial provided important data on the effects of the various interventions on diabetic retinopathy, confirming the importance of intensive glycemic control in diminishing the progression of retinopathy. In addition, it provided evidence of a protective effect of fenofibrate treatment on the same retinopathy endpoint. However, the apparent paradoxical effects of intensive glycemic control on macrovascular and microvascular disease suggests caution in the care of persons with type 2 diabetes who are judged to be at high risk for cardiovascular events.

We have been bombarded by reports from the large randomized ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial concerning the higher mortality in those type 2 diabetic patients who were randomized to intensive therapy for glycemia compared with those randomized to standard therapy[1], and the apparently inconsistent effects of intensive control on microvascular outcomes.[2] The ACCORD trial enrolled 10,251 patients with type 2 diabetes, high hemoglobin A_{1c} (HbA_{1c} ≥7.5%), and cardiovascular disease or more than 2 cardiovascular risk factors and randomly assigned these persons to intensive glycemic control (HbA_{1c} <6.0%) or standard care (to achieve HbA_{1c} 7.0%–7.9%). There was randomization within these arms to intensive treatment of blood pressure and lipid treatment. Microvascular endpoints were measures of kidney function, diabetic eye complications, and peripheral neuropathy. The primary microvascular outcome based on all ACCORD participants was the development of predefined renal failure or retinal photocoagulation or vitrectomy for diabetic retinopathy, all assessed with standard procedures. At the time of the transition from the glycemia trial, there was no significant effect of intense glycemic control on the combined microvascular endpoint of advanced renal or eye complications.[2]

These results seem to fly in the face of the findings from UKPDS (United Kingdom Prospective Study of Diabetes),[3] in which there was a demonstrated benefit of glycemic control on microvascular complications despite a smaller reduction in HbA_{1c}. Of note is that the UKPDS treatment was for 11 years. Is the conclusion to be drawn from the ACCORD trial that intense glycemic control does not benefit microvascular disease in general and retinopathy in particular? Is the data from the full ACCORD trial adequate to answer this question? In particular, is it possible that the length of the ACCORD trial, either when the transition occurred (median of 3.7 years) from the glycemia trial or even 18 months after when

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glycemia levels between the 2 groups were very similar, was insufficient to determine the effects of glycemia on relatively uncommon microvascular outcomes? In my view, the answer is yes. Post-hoc power analysis for the primary composite endpoint was 66% to detect a 15% risk reduction at transition.[2] In fact, even though the differences were not significant, by the study end those who had been on intensive control were slightly more protected against the composite microvascular endpoint than the conventionally treated subjects.[2] This is reminiscent of the "metabolic memory" concept from DCCT (Diabetes Control and Complications Trial) where there was residual effect of tight glycemic control on retinopathy that persisted after the glycemia trial was discontinued.[4] Similar findings were reported for those persons who had participated in UKPDS[5] and in another study in Denmark.[6]

Another study within the ACCORD trial gives further data to permit evaluation of these perplexing issues. ACCORD-Eye is a subgroup study of the larger ACCORD trial.[7] A sample of 4065 of the 10,251 participants in the ACCORD was targeted for the eye study; complete data were obtained for 2856 subjects. In this substudy, a more comprehensive ophthalmic examination was performed on the study subjects. This included pupil dilation and fundus (retinal) photography done according to the protocol by skilled ophthalmic photographers. The images were graded by a standardized, well-accepted team who were trained in the grading protocol, and codified quality control procedures were carried out throughout the study. Results of gradings provided objective measures of change in the severity of retinopathy between the 2 study visits 4 years apart. There was a significant difference in three-step progression of retinopathy between those with intense glycemic control compared with those with standard care; adjusted odds ratio (OR) was 0.67 (95% confidence interval [CI] 0.51–0.87; P = 0.0025). Why is this finding from a subgroup so striking while the finding from the larger study was more equivocal? The larger trial relied on more severe ocular outcomes, rarer events than were used as an endpoint of the ACCORD-Eye; thus, sample size may have played a role. Fundus photography permits the detection of smaller changes and across a range of severities. A patient with no retinopathy or mild to moderate retinopathy at baseline can sustain progression, even quite remarkable progression, but not cross the threshold for needing vitrectomy or retinal photocoagulation treatment. Progression along a finer scale could not be detected in the larger trial. The greater number of persons in the entire ACCORD trial is not sufficient to overcome that disadvantage. Severe visual impairment in one or both eyes as an endpoint to mark increased severity of diabetic ocular disease, not unexpectedly, was an infrequent outcome in the ACCORD trial and did not differ between the 2 glycemia groups. Loss of vision, especially severe loss of vision, is fortunately an uncommon event in any of the previous studies of glycemia and retinopathy, and is too insensitive a measure to evaluate functional change in vision. Even in the ACCORD-Eye, where a more moderate change in visual acuity was an outcome, there was no significant difference between the glycemia groups. The relatively short period of time militated against finding such functional changes between the 2 glycemia groups. Furthermore, decreased vision commonly occurs due to development or progression of cataract. While neither the parent ACCORD trial nor ACCORD-Eye had objective measures of cataract, cataract surgery was 11% less common in those with intensive control than in those with standard control, and this difference was significant by the end of the study.[2]

The ACCORD-Eye provided interesting information on the potential protective effect of another intervention, namely fenofibrate. There were to be 5518 persons with dyslipidemia in the larger ACCORD trial; 1593 of them were in ACCORD-Eye. All persons in the dyslipidemia trial were treated with simvastatin, but the addition of fenofibrate was done by random assignment to half of them.[8] There was a decrease in serum triglycerides of about 20 mg/dl in the fenofibrate group as compared with the control group over the first year of the study (P <0.0001) that was maintained through the end of the study. These effects were associated with reduced odds of progression of retinopathy in the fenofibrate group (OR = 0.60, 95% CI: 0.42–0.87, P = 0.0056). Prior to this, the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study had found a protective effect of fenofibrate on laser treatment for proliferative diabetic retinopathy although there was no apparent effect of serum triglyceride levels.[9] The reduction was mainly caused by a reduction in macular edema,[10] a common cause of loss of vision in those with long-term diabetes. In support of the fenofibrate finding is that clofibrate, another fibrate, was shown to be associated with improvement in retinal hard exudates in the 1960s.[11]

ACCORD-Eye offered little guidance concerning the relationship of treatment of hypertension to the progression of diabetic retinopathy. This is not surprising in view of the delayed effect that blood pressure control has had in other trials such as UKPDS.[12] Also, ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) did not show a beneficial effect of blood pressure control on progression of retinopathy[13] with odds of progression in the intensive arm being 1.23 times (95% CI 0.84–1.79) that of the standard care group. Further longitudinal follow-up will be important in trying to understand the current finding. We must remember that the current ACCORD trial reports are based on a truncated time frame. In any case, despite the finding of no effect on retinopathy, the benefits of blood pressure control on the vascular system in general has

been shown time and time again to be important in those with and without diabetes.

In summary, what conclusions can we draw from the ACCORD trials? It seems that fenofibrate on a background of simvastatin may play an important role in decreasing the progression of diabetic retinopathy, and the FIELD study seems to corroborate this beneficial effect on retinopathy. However, further clinical trial evidence confirming this regimen would, in my view, be needed before recommending this for reducing the risk of progression of retinopathy in all persons with type 2 diabetes because the participants in the ACCORD trial were a selected group of patients with long-term type 2 diabetes who were specifically recruited for their high risk of subsequent cardiovascular disease; thus, they may not represent the current impending wave of new patients with type 2 diabetes. Concerning the role of glycemia in microvascular disease as manifest in the eye, the ACCORD-Eye trial data strongly support the role of hyperglycemia in the progression of diabetic retinopathy and suggest that the more normal the level of glycemia, the lower the risk to the microvasculature. The advice of the study authors to exercise caution in the pursuit of glycemic control in persons with relatively long duration of type 2 diabetes who have cardiovascular risk factors other than diabetes is imperative. One cannot, however, treat solely with an eye to the eye.

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ARTYKUŁ POGLĄDOWY

Rozwój retinopatii u chorych na cukrzycę typu 2 – czy nowe dane prowadzą do tych samych wniosków?

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SŁOWA KLUCZOWE

cukrzyca typu 2, glikemia, retinopatia cukrzycowa

STRESZCZENIE

Badanie ACCORD (Action to Control Cardiovascular Risk in Diabetes) zaprojektowano przede wszystkim w celu oceny wpływu intensywnej kontroli glikemii na występowanie zdarzeń sercowo-naczyniowych u chorych na cukrzycę typu 2, u których z powodu występowania dodatkowych czynników to ryzyko było zwiększone. W badaniu oceniono również wpływ interwencji dotyczących kontroli ciśnienia tętniczego oraz stężeń lipidów surowicy na te same punkty końcowe. Badanie interwencji w zakresie kontroli glikemii zakończono przed zaplanowanym terminem z powodu stwierdzenia znamiennego wpływu tej interwencji na śmiertelność. Badanie dostarczyło ważnych danych dotyczących znaczenia różnych interwencji dla rozwoju retinopatii cukrzycowej, potwierdzając znaczenie intensywnej kontroli glikemii w hamowaniu postępu retinopatii. Ponadto pozwoliło udokumentować ochronny efekt leczenia fenofibratem w odniesieniu do retinopatii. Jednakże widoczny, paradoksalnie inny wpływ intensywnej kontroli glikemii na powikłania makro- i mikronaczyniowe, wskazuje na potrzebę zachowania ostrożności u chorych na cukrzycę typu 2, u których ryzyko zdarzeń sercowo-naczyniowych ocenia się jako duże.

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